Running title: Endometriosis and the risk for miscarriages

Endometriosis, especially mild disease: a risk factor for miscarriages

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Abstract

Objective: To investigate the prevalence of miscarriage in women with endometriosis (WwE) compared to disease-free control women (CW).

Design: Cross-sectional analysis nested in retrospective observational study (n = 940).

Setting: Women recruited in 9 Swiss, German and Austrian hospitals and associated private practices.

Patient(s): Previously pregnant women (N= 268) within reproductive age in matched pairs.

Intervention: Retrospective analysis of surgical reports and self-administered questionnaires.

Main Outcome Measure(s): Rate of miscarriage, subanalysis for fertility status (≤12 vs. >12 months time to conception), endometriosis stages (rASRM I/II vs. III/IV) and phenotypic localisations (superficial peritoneal SUP, ovarian OMA and deep infiltrating DIE endometriosis).

Result(s): The miscarriage rate is higher in WwE 35.8% (29.6-42.0) compared to CW 22.0% (16.7–27.0); adjusted incidence risk ratio (IRR) of 1.97 (95% CI 1.41–2.75); p <0.001. This remained significant in subfertile WwE 50.0% (40.7–59.4) vs. CW 25.8% (8.5–41.2); p = 0.017, but not in fertile WwE 24.5% (16.3–31.6) vs. CW 21.5% (15.9–26.8); p = 0.548. The miscarriage rate was higher in women with milder forms rASRM I/II 42.1% (32.6–51.4) vs. rASRM III/IV 30.8% (22.6–38.7), compared to 22.0% (16.7–27.0) in CW; p <0.001, and in women with SUP 42.0% (32.0–53.9) compared OMA 28.6% (17.7–38.7) and DIE 33.9% (21.2–46.0) compared to CW 22.0% (16.7–27.0); p = 0.005.

Conclusion(s): Mild endometriosis, as in superficial lesions is related to a great extent of inflammatory disorder, possibly leading to defective folliculogenesis, fertilization and/or implantation presenting as increased risk of miscarriage.

Trial registration number: NCT 02511626.

Key Words: endometriosis, miscarriage, infertility, pregnancy outcome, superficial peritoneal endometriosis

Introduction

Endometriosis is a chronic and often progressive disease, which is defined by endometriotic tissue outside the uterine cavity that is sensitive to cyclic steroid hormone regulation (1-3). With a prevalence of 6 - 10% of the female population, it is one of the most important benign gynecological diseases in women in their reproductive age (4). Endometriosis is associated with dysmenorrhea, dyspareunia, or chronic pelvic pain. Endometriosis is known to reduce female fertility (4-6) and has an impact on the obstetric outcome of affected women (7-10). In WwE multifactorial reasons result in a reduction in fertility: Reduced tubal motility and passage (11,12), inhibiting inflammatory factors deriving from the peritoneal fluid (13), and a diminished quality of the oocytes affect the chances of a successful implantation after natural conception as well as after assisted reproductive technology (ART) (14-17). However, not all the underlying mechanisms are yet fully understood. Over the last few years, the improvements in pharmacological, surgical, and ART treatment led to an increasing number of pregnancies in WwE (18). The success of pregnancy depends on the placentation and the endometrial function later in pregnancy (19,20). Abnormal local estrogen production and an altered endometrial response to progesterone (progesterone resistance) result in a changed microenvironment. This coats the embryo in early pregnancy (21,22) possibly affecting the "quality of implantation". Miscarriage is the most common complication during the first trimester with an incidence rate of 30 - 50% in the general population, depending primarly on the age of the women (23,24). There is no conclusive answer to the question of whether or not miscarriage rates are increased in WwE: Earlier clinical studies investigated primarily the effect of surgical treatment (ablation of endometriotic lesions) on the prevalence of pregnancy complications; these studies were not adjusted for age (25-27). Some newer studies considering age as a risk factor and showed an association of endometriosis with previous pregnancy losses (8,9,28), but others did not (7, 30-32). A large Canadian cohort study over 12 years with registry data from 784 WwE and 30,284 CW reported a significantly higher rate of miscarriages in WwE (odds ratio 1.89, 95% CI 1.23 – 2.93); however, the diagnostic quality of endometriosis was limited (8). The most recent study on previously

pregnant women with and without endometriosis was conducted at a specialized referral center. It found a higher miscarriage rate in endometriosis-affected women 29.1% (23.9 – 34.3) compared to control women 19.4% (16.1 – 22.7), p = 0.001 (7). Because of the high number of women with progressive disease (several surgeries before inclusion in the study) and severe endometriosis lesions, women with mild or asymptomatic disease were rather underrepresented in this collective.

Our primary aim was to evaluate and compare miscarriage rates in a population of women with surgically confirmed endometriosis and a broad variety of clinical manifestations; in order to reflect the average female population affected by endometriosis. To improve our understanding of the association between endometriosis and miscarriage, we included in the analysis the phenotypical disease localization and the fertility status.

Methods

This is a cross-sectional analysis about the prevalence of miscarriages nested in a retrospective observational study (n = 940) on the quality of life in WwE.

Questionnaire

We designed a questionnaire focusing on the women's health and obstetric history. We collected sociodemographic data and asked the women whether or not they had difficulties conceiving and for how long they tried to become pregnant.

Recruitment

Women from the ages of 18 to 45 were recruited between December 2010 and December 2015 at participating hospitals or associated private practices. Participants were recruited at university hospitals in Switzerland, Germany and Austria (University Hospital Zurich, Charité – Medical University Berlin, University Hospital of Graz, and RWTH Aachen University), cantonal hospitals in Switzerland (Schaffhausen, Winterthur, St. Gallen, Solothurn), the Stadtspital Triemli Zurich and in associated private medical practices. Inclusion criteria were

defined as not being pregnant and being able to complete the questionnaire (without linguistic, mental or psychological impairment). Patients having undergone surgery for the diagnosis of endometriosis and fulfilling inclusion criteria were invited to participate and asked for informed consent. CW without clinical suspicion of endometriosis (no severe dysmenorrhoea, no heavy cyclic abdominopelvic pain) fulfilling the inclusion criteria were recruited during annual check-ups. In total 647 women affected by endometriosis and 666 CW were invited to participate. Of those invited, written consent was received from 505 WwE (78.0%), and 435 CW (65.3%) respectively.

Surgical reports

Surgical reports for each surgical intervention were obtained from the patients' clinics. From 468 out of 505 WwE (92.7%), we obtained surgical reports with sufficient details to do a correct staging and grading of the lesions. In 438 of 468 WwE (93.6%), the diagnosis was confirmed histologically after surgical resection; 30 of 468 WwE (6.4%) were diagnosed surgically, primarily after laser evaporation of light lesions. To avoid bias, all surgical and histological records were reviewed by two blinded investigators.

The documents reviewed contained the total number of endometriosis-associated surgeries, the histological confirmation of endometriosis, a description of the localization and size of endometriosis lesions and the dimensions of adhesions. The revised classification of the American Society for Reproductive Medicine (rASRM) (33) was used to categorize the endometriosis into the four stages. This staging was applied, as it was initially developed to define chances for pregnancy (34). Additionally, the lesions were classified into three phenotypes: superficial peritoneal endometriosis (SUP), ovarian endometriosis (OMA), and deep infiltrating endometriosis (DIE), as previously described by other investigators (35,36). DIE lesions were classified as ≥ 5mm deep invasive endometriotic lesions. (2,37). As those three different phenotypes often present together, patients were classified according to their most severe lesion, used for grading as follows: DIE >OMA >SUP (35,38).

146 Statistical analysis

147 We analyzed responses regarding the number of previous miscarriages, the number of
148 pregnancies conducted beyond the 24th gestational week, and the number of deliveries.
149 All data were stored in a computerized database. Statistical analysis was performed using
150 STATA statistical software Version 14 (Stata Corporation, College Station, TX, USA). Data
151 were presented as absolute numbers (n) and as percentages, with 95% confidence intervals
152 (95% CIs). Differences among groups were analyzed by chi-square tests for categorical data;
153 the Student's t-test was used for quantitative data. Miscarriage rates were defined as the
154 rate of previous failures relative to the total number of previous pregnancies. We calculated
155 the miscarriage rate for the rASRM stages and the most severe phenotypic endometriosis
156 localization in fertile and subfertile subpopulations. Adjustments were made for known risk
157 variables: age (≤29, 30-35, ≥35 years), BMI (≤19, 20-24, 25-29 and ≥30 kg/m^2) and smoking
158 (never a smoker, previous smoker, and current smoker) as categorical variables. Due to
159 missing values (18/268), multiple imputations were made for "smoking". "Previous
160 miscarriage" is not independent in our population, because women can have more than one
161 miscarriage. Therefore, we applied a hierarchical mixed effect model (Poisson regression) to
162 account for the matched pairs (level I) and for pregnancies within the same woman (level II).
163 We calculated the rate of miscarriages/pregnancies within our population (39). The model
164 was chosen because each event has a defined onset (pregnancy) with a defined endpoint
165 (miscarriage or delivery). The level of significance was set at $p < 0.05$ and $p < 0.001$ for
166 multiple testing.
167
168 Ethics
169 The regional ethical review committees as well as the ethic boards of the participating
170 hospitals in Switzerland, Germany, and Austria approved the study. All women provided
171 signed informed consent for study participation as well as verification of endometriosis
172 diagnosis through their medical charts. The trial was conducted in accordance with the

Declaration of Helsinki. It was registered at clinicaltrials.gov, under the reference number NCT 02511626.

Results

Study population

For this analysis, woman with previous pregnancies were selected as shown in Figure I. In the final analysis we included 143 WwE matched for age with 143 CW, out of 203 (total n = 286). Most WwE were born within 12 months of their matching CW (120 pairs) the remaining were born at most 24 months apart (23 pairs). Of the 286 women, a total of 508 previous pregnancies was analyzed.

Patient characteristics of 143 WwE and 143 CW were analyzed (Table 1). There were no significant differences in the characteristics of the two groups beside the lower parity in WwE: a total number of 152 children were delivered by WwE, compared to 204 children born of CW; 32 WwE (22.4%) and 13 CW (9.1%) were nulliparous; p = 0.001.

Among WwE, 33 were staged with rASRM I (23.1%), 26 with rASRM II (18.2%), 42 with rASRM III (29.4%) and 42 with rASRM IV (29.4%). The phenotypically most severe endometriosis lesion was a SUP in 48 women (33.6%), an OMA in 47 women (32.8%), and a DIE in 48 women (33.6%). Of the 48 women with DIE, 33 had cul de sac lesions, 11 had an invasive lesion on the sacrouterine ligament and 4 had invasive peritoneal lesions of other localisations. The mean number of surgical interventions related to endometriosis per WwE was 1.87 (range 1-9).

Miscarriages

In our analysis, 240 pregnancies in WwE and 268 pregnancies in CW were included (Figure I). The total number of miscarriages per woman was similar in both groups: 36 WwE and 30 CW had one previous miscarriage; 13 WwE and eight CW had two previous miscarriages. Recurrent miscarriages, with three or more miscarriages (according to the ESHRE

classification, 40), occurred in a total of 11/286 (3.9%) women, 7/143 (4.9%) WwE, and 4/143 (2.8%) CW, p = 0.874.

Table 2 shows miscarriage rates in relation to fertility, localization of the most severe lesions, and disease stage. Generally, the miscarriage rate was significantly higher in WwE compared to CW (Table 2). This difference remained significant for subfertile women independent of previous ART, but the miscarriage rate for fertile WwE did not differ from the miscarriage rate for fertile CW.

Mild and severe endometriosis were both associated with a higher prevalence of miscarriages compared to CW. This relationship was stronger in mild endometriosis (rASRM I/II) than in severe endometriosis (rASRM III/IV), compared to CW. The miscarriage rate was highest in women diagnosed with SUP, followed by women diagnosed with DIE, and then by women diagnosed with OMA.

Our regression model confirmed a higher rate of previous miscarriages for WwE compared to CW (Table 3), also after adjustment for risk factors for miscarriage such as age, BMI, subfertility, and smoking habit. The adjusted IRR for previous miscarriages was significantly increased in subfertile but not in fertile WwE. The adjusted IRR for previous miscarriages was significantly higher in cases of mild and of superficial peritoneal endometriosis compared to CW.

Discussion

This study shows a higher rate of previous miscarriages in WwE, especially in women with minimal or mild disease, compared to CW in the adjusted analysis. We show that primarly women with milder forms of endometriosis as well as subfertile woman are affected by miscarriages. This allows a clearer picture among different types of endometriosis and indicates that the diagnosis of endometriosis should not generally be associated with a higher risk for miscarriage. It also means that young women with early stages of endometriosis, a good ovarian reserve and tube motility should be reassured and encouraged to try for a spontaneous conception.

A strength of this study is the inclusion of women recruited in secondary, and tertiary centers as well as in private practices: this distribution offers a considerably representative sample of the female population treated for endometriosis. While many women diagnosed with endometriosis suffer from severe pain symptoms and a decreased quality of life, others experience fewer pain symptoms and a quality of life similar to that of the general population (41). WwE treated in secondary and tertiary centers seem to differ in disease symptoms and associated quality of life (42) from women treated in primary care centers. As most studies focus on the presence of disease symptoms, WwE with few symptoms and satisfactory quality of life are underrepresented in most scientific studies conducted at universitary care centers. Our recruitment strategy was applied to overcome this selection bias and reflect the average female population affected and treated by endometriosis.

Because of the heterogeneity of endometriosis lesions, classification systems often show only weak associations with disease symptoms (41). Another strength of this study, is the application of both the well-known classification system of the American Society for Reproductive Medicine (rASRM; 33) and the surgical phenotypic classification of endometriosis adopting the description of the most severe endometriosis lesion (SUP <OMA, <DIE) (36). It has been shown that phenotypic classification corresponds better to the obstetric outcome than the rASRM classification (42,43). The even distribution of SUP, OMA, and DIE as the most severe localization of the endometriosis disease within our study population allows for a reliable evaluation of the role of different lesion locations in the risk for miscarriage.

Furthermore the analysis based on the mixed-effects Poisson regression model accounting for the non-independence of pregnancies within the same women delivers very reliable results. Recall bias was minimized through the selection of women with previous pregnancies for evaluation within an observational study on quality of life in WwE, e.g. the women were not aware of this particular investigation's hypothesis. The sample size was

large and the age ranges particularly narrow: matching in the present study provided a control sample out of the same population. This is particularly important because age is the most important risk factor for miscarriages.

The following limitations have to be taken into consideration: data analysis was based on questionnaire information; beside reporting on endometriosis related surgery, no other medical records were reviewed, diagnosis of endometriosis was based on surgical and histological reports. Laparoscopy with or without histological verification is widely used to diagnose and rule out the presence of endometriosis. However, the correct diagnosis of endometriosis depends highly on the abilities of the surgeon performing the laparoscopy. Hidden endometriosis lesions retroperitoneally or vaginally can be easily missed, especially if the patient has not been thoroughly examined preoperatively (44)In the past surgical judgment was proven to be equivalent to histological diagnosis (45). Surgical and histological reports did not allow inclusion of possible adenomyotic lesions, because correct diagnosis would need specific ultrasound assessment of the uterine morphology (46). Uterine adenomyosis is known to frequently coexist with endometriosis (15) and is associated with an increased risk for miscarriages (47).

Acquired information about infertility and reasons for subfertility and ART treatment is based on the patients' answers. Pregnancy, the loss of a pregnancy and deliveries are life events, so recall is most likely correct and, if biased, then for WwE and CW in the same manner. In women affected with endometriosis, sensitivity to possible infertility might be higher, as it is known and often communicated, that endometriosis might affect fertility. This could lead to an information bias and could affect the detection of a pregnancy different from that of CW.

As a further limitation, asymptomatic endometriosis in the control group cannot be excluded, since not all of the CW had surgical treatment and were included into the study after the exclusion of symptoms suspicious for endometriosis. This recruitment was the best possible, since recruitment of women undergoing laparoscopy for gynecological non-endometriosis reasons such as e.g. tubal ligation or removal of benign ovarian cysts have an affected fertility, so they impose a selection bias. However, missed diagnosis of endometriosis in the

control group would lead to an overestimation of the described effect. The recruitment in different centres reduces selection bias in regard to similarity with the general population, both in WwE and CW. Because of the number of missing answers for thyroid disease, and immunological disorders, we could not include these specific risk factors into our mixed-effect regression model.

Our results are in agreement with large registry-based studies (8,48), showing a higher prevalence of miscarriages in women diagnosed with endometriosis than in CW. Studies showing no difference in miscarriage rates between women with and without endometriosis focus either on ART-treated women (31,32) or women with surgically treated septate uteri (30). Both of these conditions might imply a higher impact on miscarriage rates than the endometriosis itself. The following mechanisms support our results indicating an association between endometriosis and miscarriages: pathophysiologically, an impaired folliculogenesis and an insufficient endometrial function in WwE have been postulated. The eutopic endometrium may not function normally in WwE: inflammation processes lead to an increased release of reactive oxygen species (ROS) and an increased expression of enzymes (17). These enzymes induce an accumulation of free radicals in cells near and in the endometrium, which possibly affect implantation (17). Additionally, ROS affect the mitotic spindle as well as the separation of chromosomes and consequently delay completion of meiosis I during fertilization (49,50); this could provide an explanation for a lower oocyte quality in endometriosis, as shown in animal studies (51).
Physiologically, progesterone induces the decidualization of stromal cells of the endometrium to become receptive for the embryo (52). As a consequence of progesterone resistance in endometriosis, this process may become dysregulated and lead to suboptimal implantation (6). Endometriosis affected tissue shows different pathological features, for example delayed maturation, altered glycosylation and molecular abnormalities such as alterations in local steroid biosynthesis, cell growth, apoptosis, immune-cell function, angiogenesis, cell adhesion, and cytokine production, all of which might reduce chances of a successful

312 pregnancy outcome (14, 53, 54, 55). In the literature the use of anti-inflammatory hormonal
313 (56,57) and non-hormonal (58) treatments for pain symptoms have been examined. It is
314 recommended that they be investigated further for their potential to improve implantation and
315 reduce miscarriages.
316 In addition, in endometriosis inadequate uterine contractions occur throughout the menstrual
317 cycle; the frequency, amplitude and basal pressure have been shown to be higher and
318 possibly favor miscarriages (17).
319
320 The higher miscarriage rate in lower stages of endometriosis detected in our study is in line
321 with findings from other authors: the recent analysis by Santulli *et al*. (9) showed a higher
322 rate of miscarriages for all phenotypes of endometriosis e.g. SUP, OMA and, DIE compared
323 to CW. As in our study, the highest miscarriage rate was reported for “mildest” SUP lesions
324 (n = 33/87; 37.9%) vs. OMA lesions (n = 28/104; 26.9%) vs. DIE lesions (n = 78/287; 27.2%).
325 In both studies, the higher rate of previous miscarriages in women with SUP could be the
326 result of a higher pregnancy rate among these women: women with more severe lesions
327 such as OMA or DIE are more likely to have a lower reproductive performance (59,60) or
328 poor motility of the fallopian tubes (11), with consecutively lower spontaneous over all
329 pregnancy rates.
330 In contrast, a meta-analysis of reproductive outcomes by Barbosa (60) did not show a
331 significant difference in miscarriages between mild and severe endometriosis-affected
332 women. Only 21 out of 92 studies included in this meta-analysis reported rASRM staging of
333 endometriosis, so evidence in relation to ASRM staging was considered low.
334 Pathophysiological mechanisms might explain the finding of increased miscarriage rates in
335 WwE but also especially in women with mild endometriosis: early stages of the disease with
336 more active lesions are known to lead to a more inflammatory milieu (61,62), compared to
337 the more scarring lesions of higher disease stages (63). Fresh endometriosis lesions seem to
338 be associated with an inflammatory response represented by overproduction of
339 prostaglandins, metalloproteinases, cytokines, and chemokines (3). The resulting

inflammatory process impairs ovarian, peritoneal, tubal, and endometrial function, and may lead to defective folliculogenesis by altered follicular milieu because of increased rates of granulosa cell apoptosis (64) as well as increased concentrations of follicular fluid natural killer cells and lymphocytes (65), fertilization, and/or implantation (5). However it has been shown very recently, that the rate of aneuploidy rate in patients affected by endometriosis is not increased (66). This could lead us to the speculation that the impact of mild endometriosis on fertility might be due to non-genetic rather metabolic intracellular processes; so either insufficient oocyte maturation with retardation of the embryo before reaching blastocyst stage or on insufficient embryonal development either because of altered endometrial receptivity (67) and therefore reduced „supply“ or an impariment of intracellular metabolism probably also in trophoblast development.

There is an association of miscarriages in subfertile women with and without endometriosis. Additionally, subfertile women often require ART, an intervention possibly associated with complications later in pregnancy such as e.g. preterm birth and low birth weight (68). ART itself does not pose a risk for miscarriages, but the underlying specific reproductive disorders and the increased age, both affecting oocyte quality are of very high importance when assessing miscarriage risk (69) in these women.

Based on this knowledge, our results of highest IRR for subfertile women with endometriosis are not surprising. In contrast our finding that there is no difference in the prevalence of miscarriages between fertile WwE and fertile CW is very important for counseling.

Our findings are in contrast to the above-mentioned recent study (9), where the risk for miscarriages in fertile women with endometriosis (67/341; 19.6%) was significantly higher than in control women (72/583; 12.3%). However, the miscarriage rates in both of these groups were lower compared to our and other studies (70). The reason for the differences in these results might be the older age of women, e.g. the higher risk for miscarriage at the time of inclusion into our study.

In conclusion, our study found that miscarriage rates are higher in endometriosis-affected women, especially in women with mild lesions and those suffering from infertility. Further

studies, especially prospective controlled studies, are necessary to confirm our findings. A retrospective study such as this, with the attendant limitations of study design, cannot definitely prove the hypothesis. Analyzing underlying pathophysiological mechanisms such as the folliculogenesis and the endometrial function may help to better understand the etiology of miscarriages and develop effective treatments to improve chances for successful pregnancy in women with endometriosis.

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Figure legends

Figure 1

Patient inclusion flow-chart

WwE: Women with endometriosis, CW: Control women

Table 1

Patient characteristics

WwE: Women with endometriosis, CW: Control women

Data reported as mean ± standard deviation or number (%)

a: chi-square test; b: t-test

Table 2

N= number of miscarriages/ pregnancies

WwE: Women with endometriosis, CW: Control women

a: chi-square test

Rates of previous miscarriages according infertility and rates of previous miscarriages according surgery

rASRM: revised American Society of Reproductive Medicine classification (ASRM 1997)

Surgical phenotypical classification (Chapron et al. 2010)

SUP: superficial endometriosis; OMA: ovarian endometrioma; DIE: deep infiltrating endometriosis

Table 3

Incidence rate ratio (IRR) of previous miscarriages from the mixed-effects Poisson regression analysis

WwE: Women with endometriosis, CW: Control women

a: adjusted for age, BMI, smoking* habits and subfertility

*: imputation for smoking because of missing answers

rASRM: revised American Society of Reproductive Medicine classification (ASRM 1997)

Surgical phenotypical classification (Chapron et al. 2010)

SUP: superficial endometriosis; OMA: ovarian endometrioma; DIE: deep infiltrating endometriosis

Table 1

	Women with endometriosis (WwE) N = 143	**Control women (CW) N = 143**	**p- value**
Age (years)	37.34 ± 4.83	37.45 ± 4.78	0.898[a]
BMI (kg/m^2)	23.10 ± 4.24	23.47 ± 3.77	0.584[a]
Smoking habits (n, %)			
Never smoked	66 (46.1%)	77 (53.8%)	0.301[a]
Previous smoker	46 (32.2%)	37 (25.9%)	
Current smoker	23 (16.1%)	18 (12.6%)	

Not available		8 (5.6%)	11 (7.7%)	
Gravidity (n, %)				
	1	83 (58%)	64 (44.7%)	**0.071[a]**
	2	37 (29.5%)	52 (36.4%)	
	≥3	23 (16.1%)	27 (23.9%)	
Parity (n, %)				
	0	32 (22.4%)	13 (9.1%)	**0.001[a]**
	1	75 (52.4%)	67 (46.8%)	
	2	31 (21.7%)	52 (36.4%)	
	≥ 3	5 (3.5%)	11 (7.7%)	
Immunological disease (n,%)		14 (9.8%)	7 (4.9%)	0.890[b]
Thyroid disease (n, %)		22 (15.4%)	19 (13.3%)	0.377[b]

Table 2

	Endometriosis women (WwE) (total N= 240)		Control women (CW) (total N= 268)		
	N	Rate % (95% CI)	N	Rate % (95% CI)	p- val[a]
Total	86/240	35.8 (29.6 – 42.0)	59/268	22.0 (16.7 – 27.0)	<0.001
Fertile women	32/132	24.5 (16.3 – 31.6)	51/237	21.5 (15.9 – 26.8)	0.548
Subfertile women	54/108	50.0 (40.7 – 59.4)	8/31	25.8 (8.5 - 41.2)	0.017
Previous ART	11/20	55.0 (36.5 – 76.8)	1/19	5.3 (0.1 – 15.3)	<0.001

SUP		OMA		DIE		Controls		
N	Rate % (95% CI)	N	Rate % (95% CI)	N	Rate % (95% CI)	N	Rate % (95% CI)	p- val[a]
34/79	43.0 (32.0 – 53.9)	22/77	28.6 (17.7 – 38.7)	20/59	33.9 21.2 – 46.0)	59/268	22.0 (16.7 – 27.0)	0.005

rASRM I/II		rASRM III/IV		Controls		
N	Rate % (95% CI)	N	Rate % (95% CI)	N	Rate % (95% CI)	p- val[a]
45/107	42.1 (32.6 – 51.4)	41/133	30.8 (22.6 – 38.7)	59/268	22.0 (16.7 – 27.0)	<0.001

Table 3

	Unadjusted IRR (95% CI)	p-value	Adjusted[a] IRR (95% CI)	p-value
CW	Ref		Ref	
All WwE	1.62 (1.17 – 2.27)	0.004	1.97 (1.41 – 2.75)	<0.001
Subfertile CW	Ref		Ref	
Subfertile WwE	1.94 (0.92 – 4.07)	0.081	2.41 (1.01 – 5.78)	0.048

Fertile CW	Ref		Ref	
Fertile WwE	1.13 (0.72 – 1.75)	0.597	1.11 (0.7 – 7.76)	0.657
CW	Ref		Ref	
WwE with rASRM lesion I/II	1.91 (1.29 – 2.82)	0.001	1.57 (1.00 - 2.44)	0.046
WwE with rASRM lesion III/IV	1.40 (0.94 – 2.08)	0.098	1.19 (0.76 - 1.85)	0.446
WwE with SUP lesion	1.98 (1.33 – 2.95)	0.001	1.67 (1.07 - 2.61)	0.024
WwE with OMA lesion	1.32 (0.81 – 2.14)	0.256	1.11 (0.65 - 1.88)	0.703
WwE with DIE lesion	1.49 (0.91 – 2.43)	0.110	1.19 (0.70 - 2.61)	0.515

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